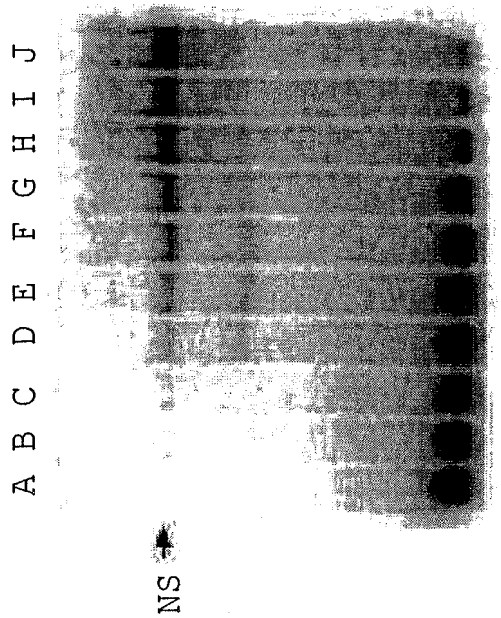


Fig. 1B

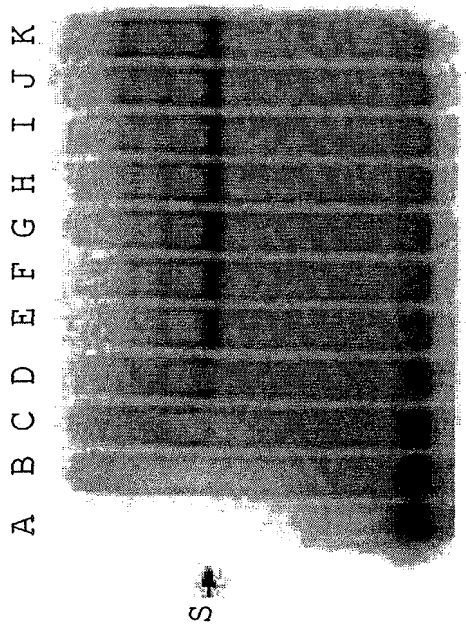


Fig. 1A

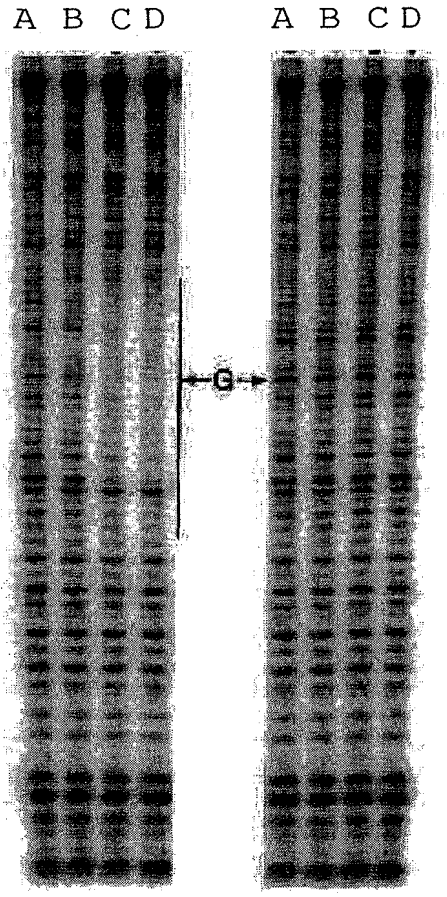


Fig. 1C Fig. 1D

FIG. 1E

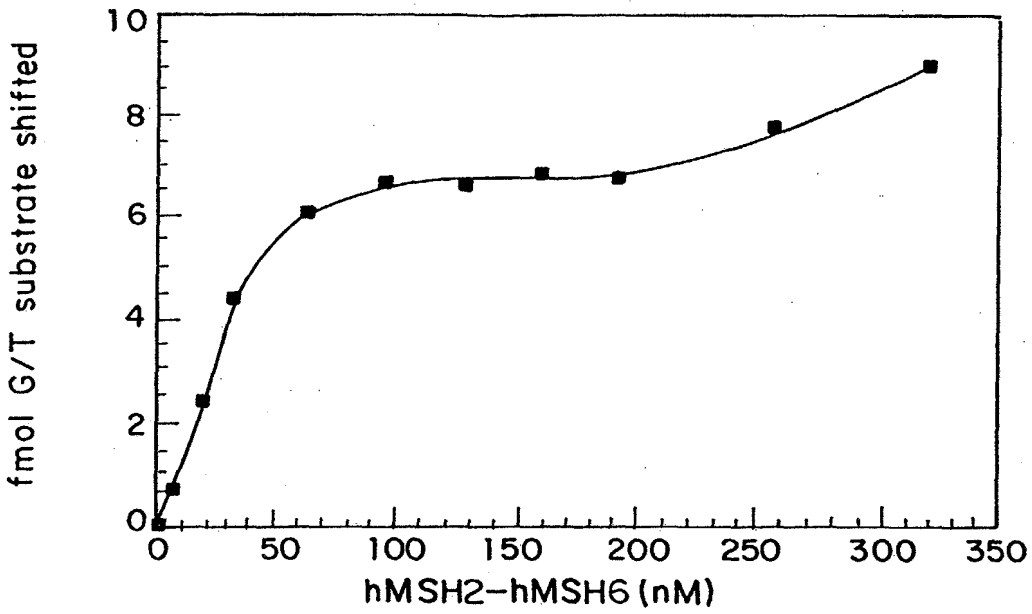
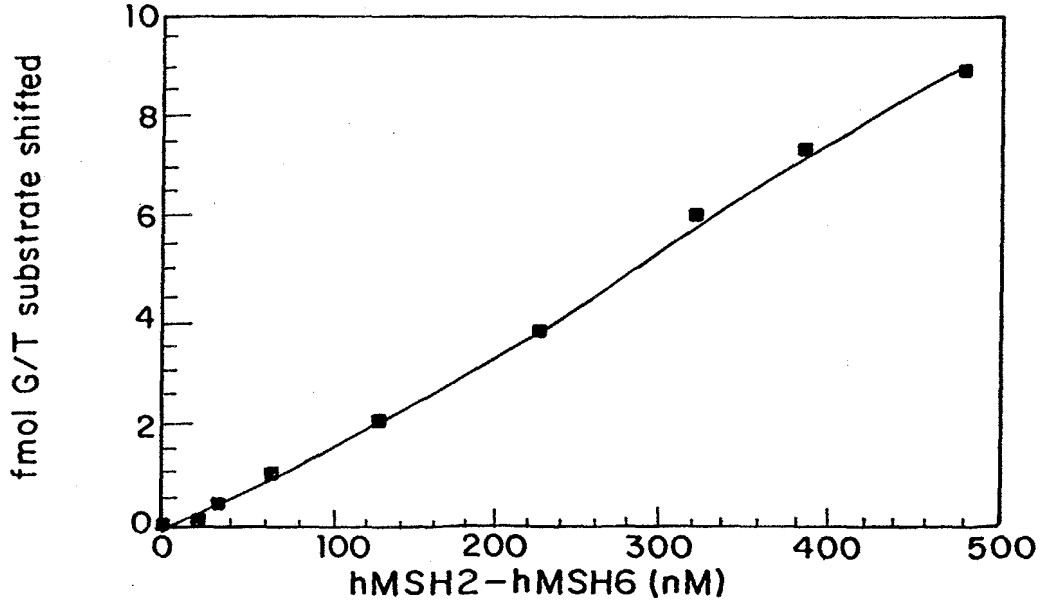

fmol G/T substrate shifted
0
2
4
6
8
10
0
50
100
150
200
250
300
350
hMSH2–hMSH6 (nM)

FIG. 1F


fmol G/T substrate shifted
0
2
4
6
8
10
0
100
200
300
400
500
hMSH2–hMSH6 (nM)

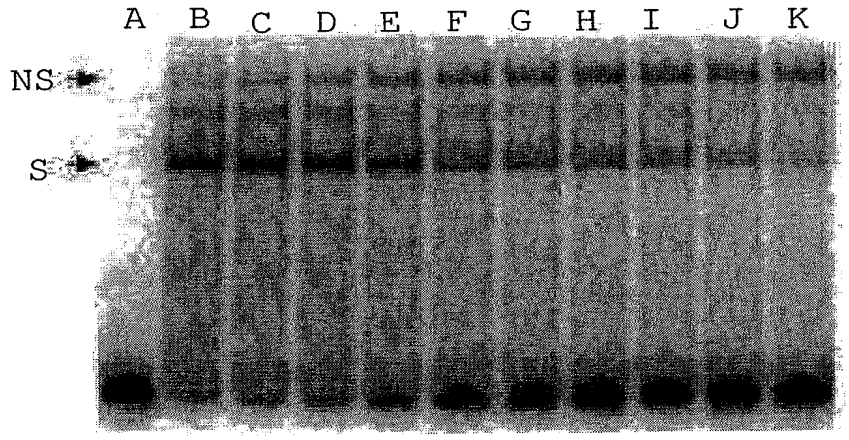


Fig. 2A

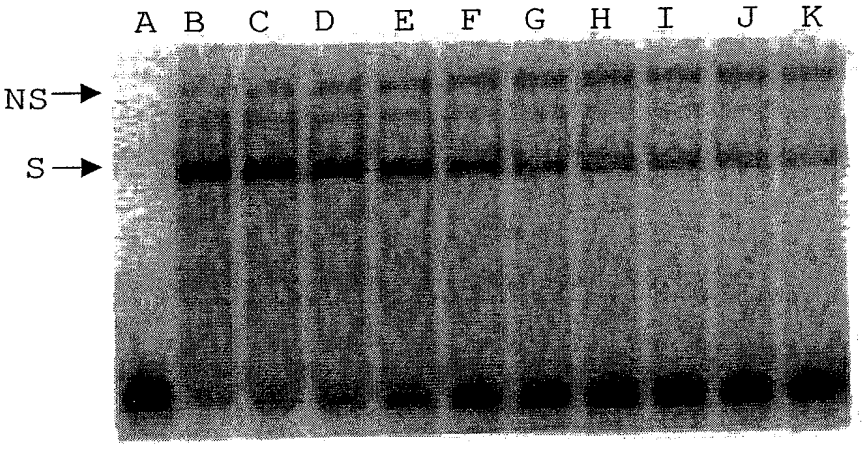


Fig. 2B

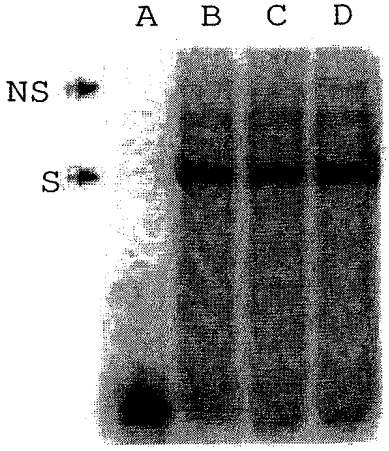


Fig. 2C

FIG. 2D

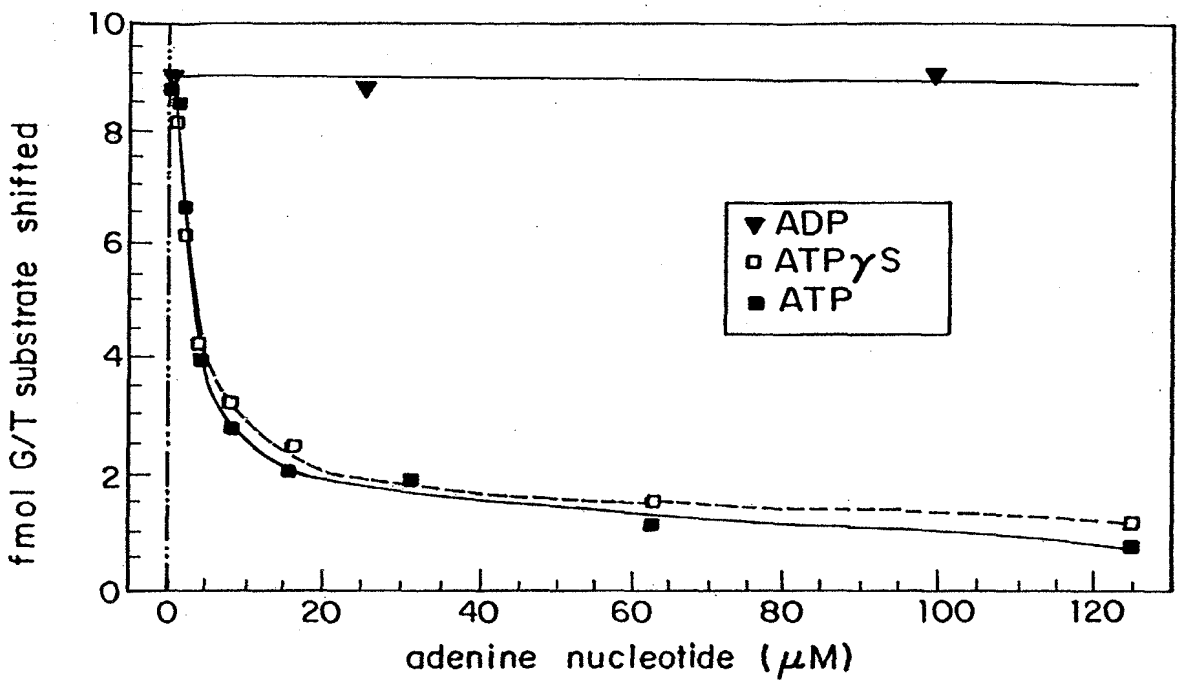

fmol G/T substrate shifted
adenine nucleotide (μM)
ADP
ATPγS
ATP
0
2
4
6
8
10
0
20
40
60
80
100
120

FIG. 3

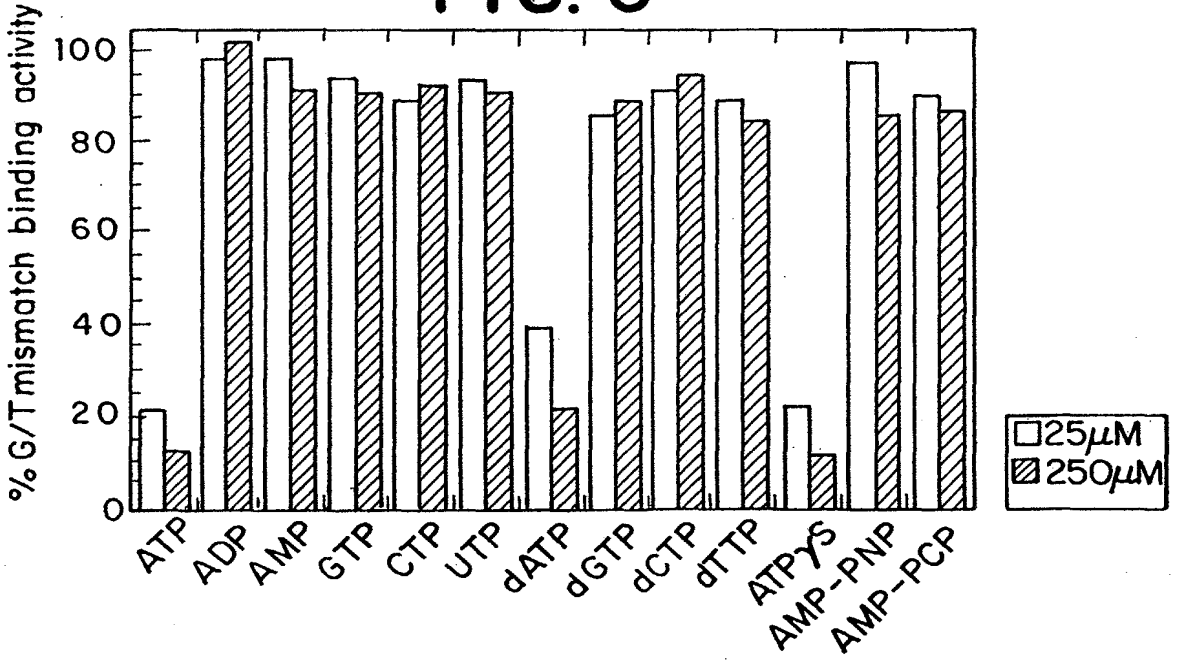

% G/T mismatch binding activity
25μM
250μM
ATP
ADP
AMP
GTP
CTP
UTP
dATP
dGTP
dCTP
dTTP
ATPγS
AMP-PNP
AMP-PCP
0
20
40
60
80
100

FIG. 4A

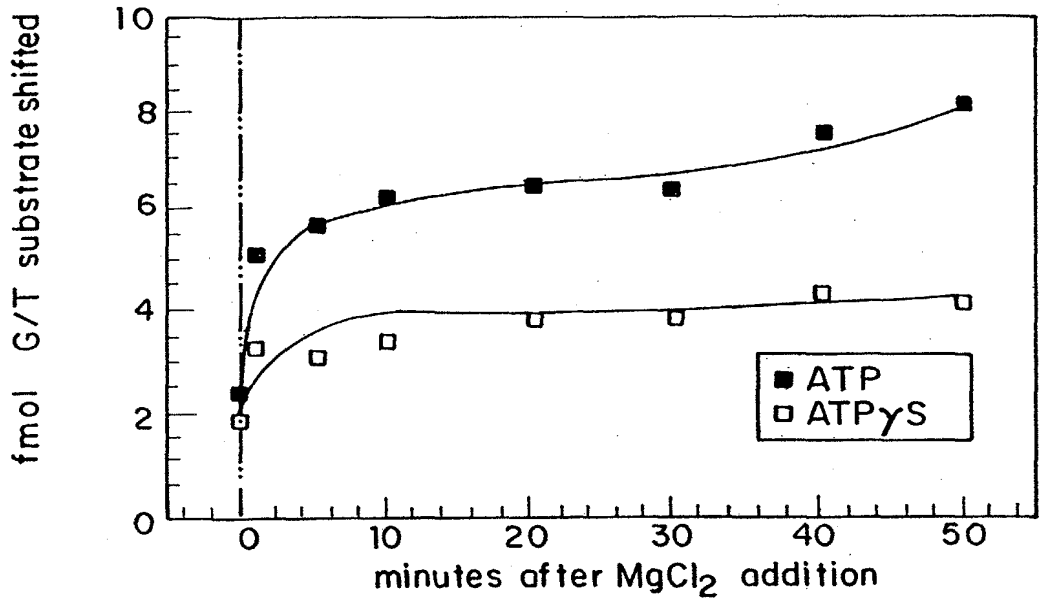

fmol G/T substrate shifted
10
8
6
4
2
0
0
10
20
30
40
50
minutes after $MgCl_2$ addition
ATP
ATPγS

FIG. 4B

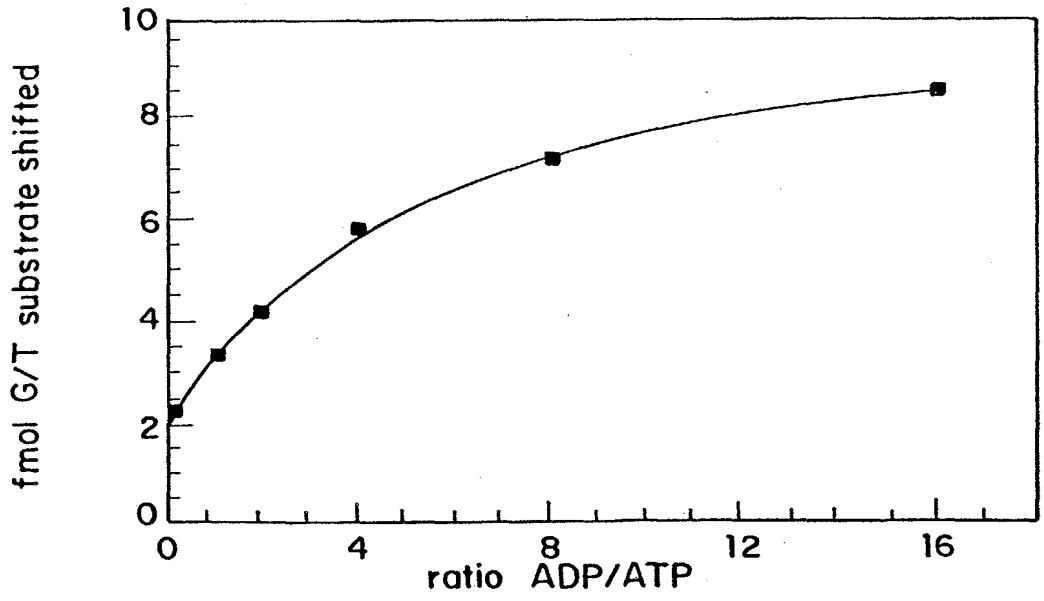

fmol G/T substrate shifted
10
8
6
4
2
0
0
4
8
12
16
ratio ADP/ATP

FIG. 5A

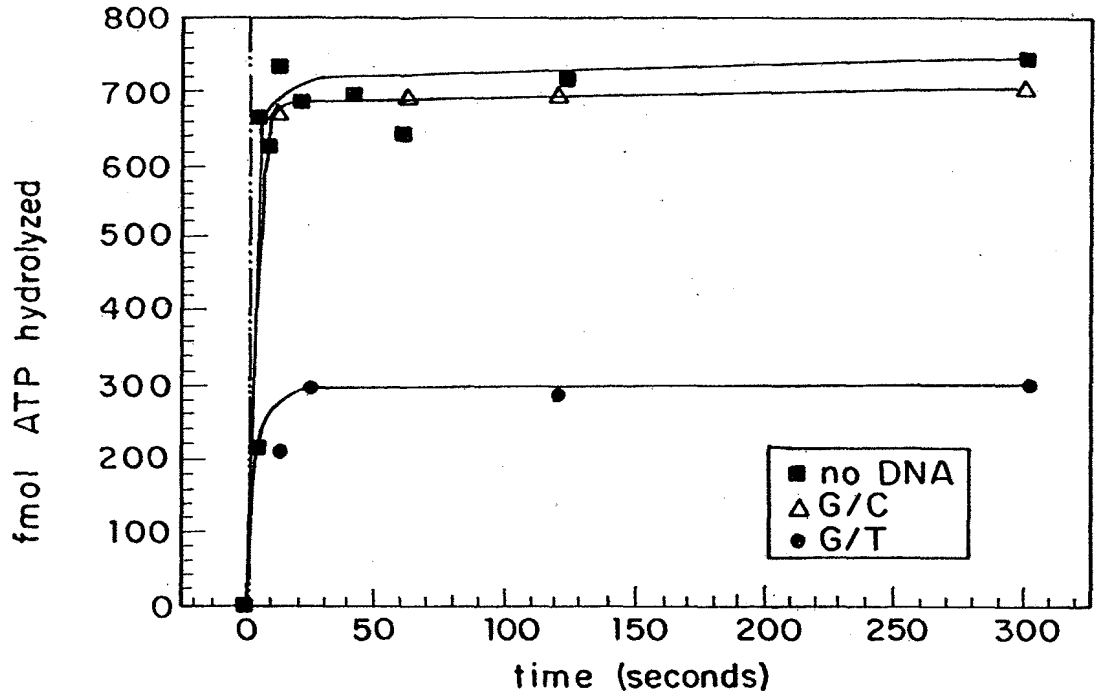
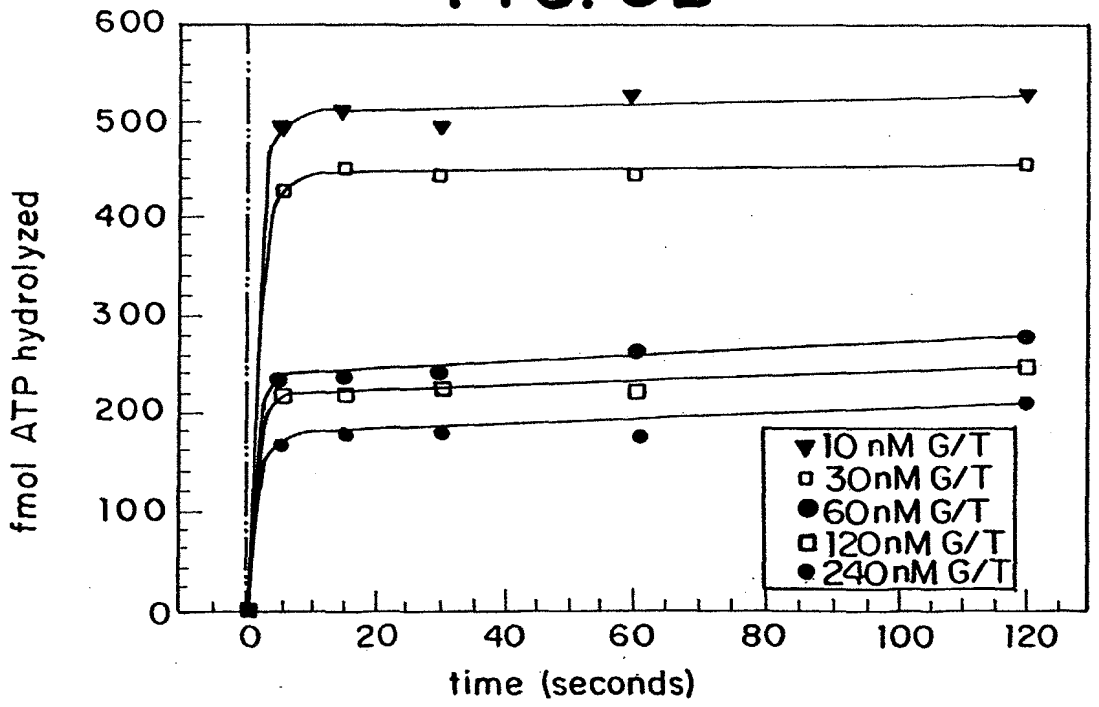


FIG. 5B



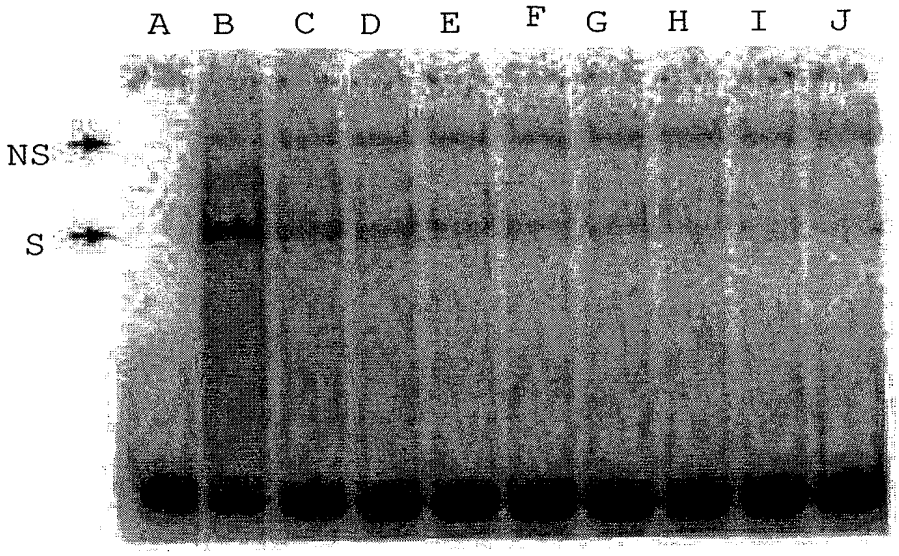


Fig. 6A

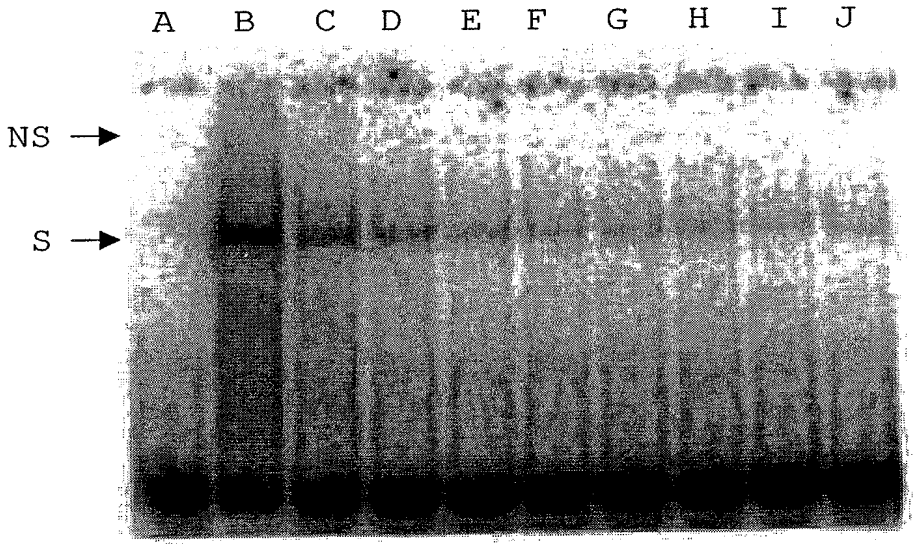


Fig. 6B

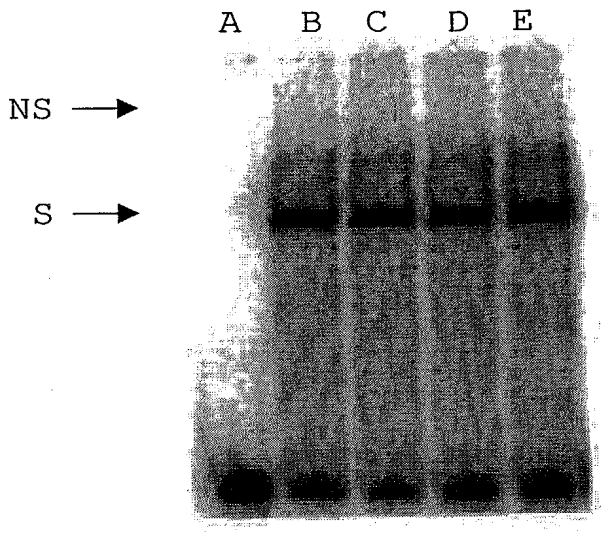


Fig. 6C

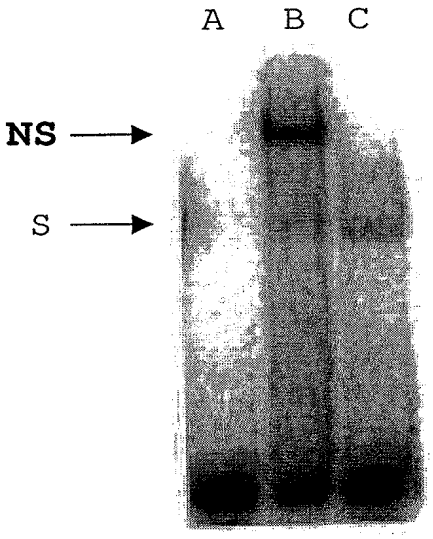


Fig. 6D

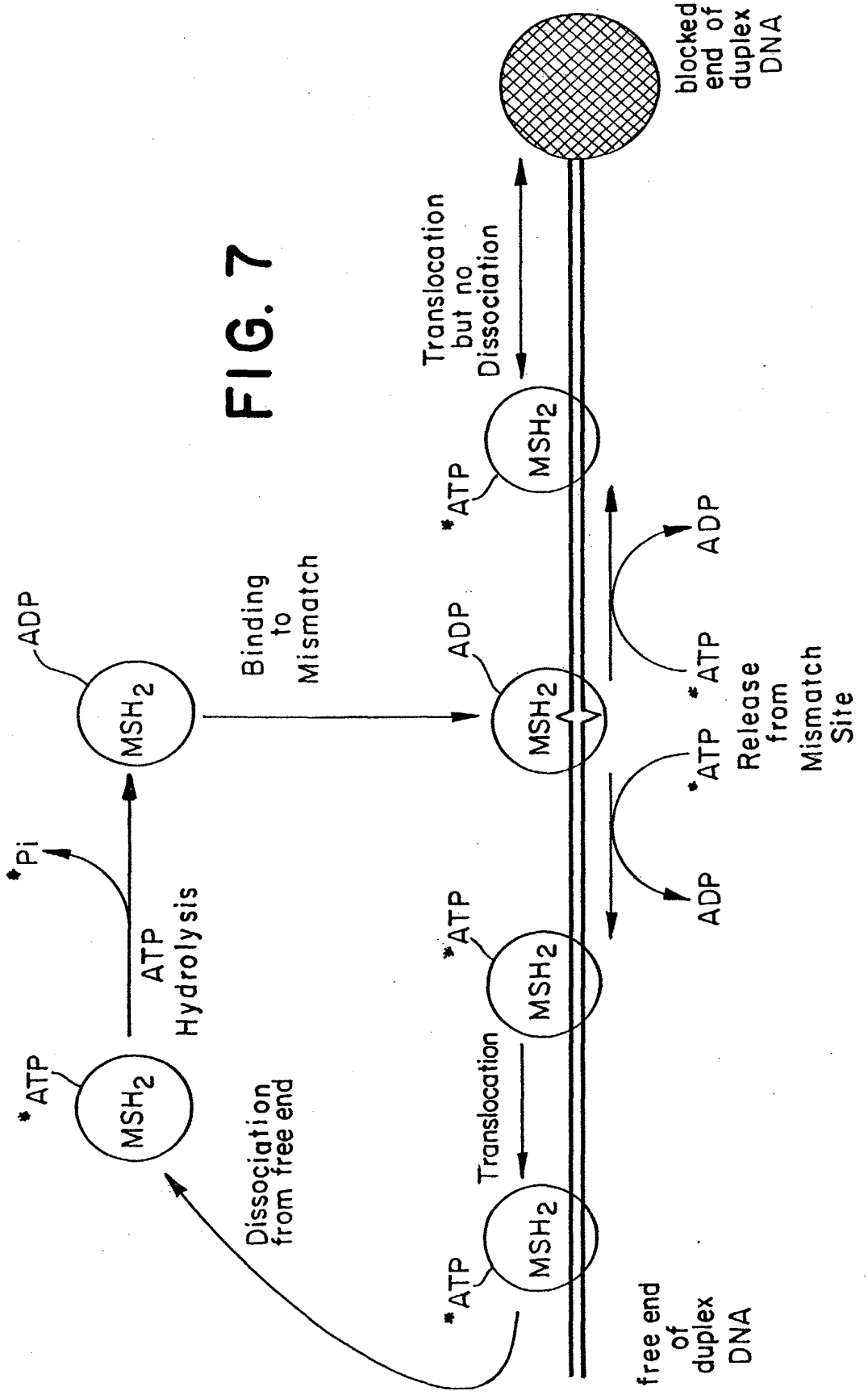

blocked end of duplex DNA
Translocation but no Dissociation
*ATP
MSH2
ADP
Binding to Mismatch
ADP
MSH2
*ATP
ADP
*ATP
Release from Mismatch Site
*ATP
MSH2
ADP
*ATP
MSH2
Translocation
*ATP
MSH2
Dissociation from free end
*Pi
ATP Hydrolysis
*ATP
MSH2
free end of duplex DNA

FIG. 7

Fig. 8A

CCTGGTACCT CGAGCGATCA AGCTTGGTGG AATTCGCCG

Fig. 8B

CCTGGTACCT CGAGCGATCG AGCTTGGTGG AATTCGCCG

Fig. 8C

ACTATAGGGC GAATTGGGTA CCGCTGAATT GCACCGAGCT CGATCCTCGA
TGATCCTAAG CTAAGCTTCA GCTCCAGCTT T

Fig. 8D

ACTATAGGGC GAATTGGGTA CCGCTGAATT GCACCGAGCT TGATCCTCGA
TGATCCTAAG CTAAGCTTCA GCTCCAGCTT T

Fig. 9A

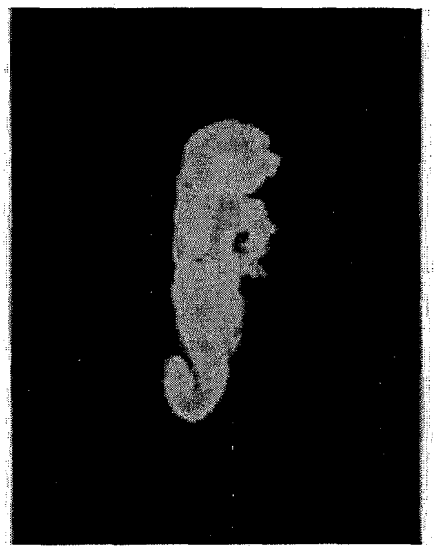


Fig. 9C

Fig. 9D

Fig. 9B

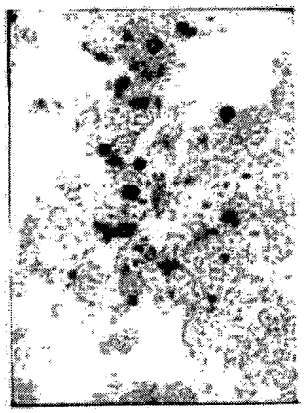


Fig. 10C

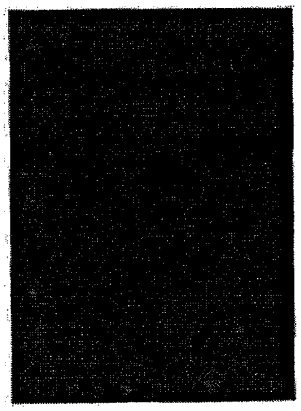


Fig. 10F

Fig. 10B

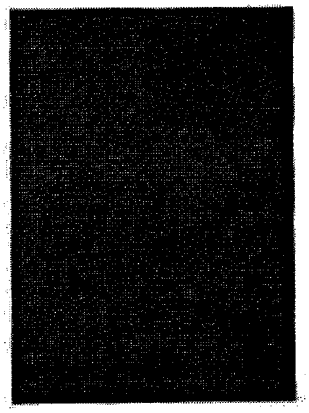


Fig. 10E

Fig. 10A

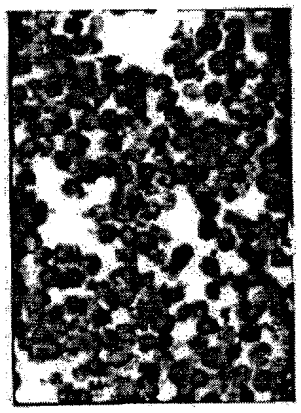


Fig. 10D

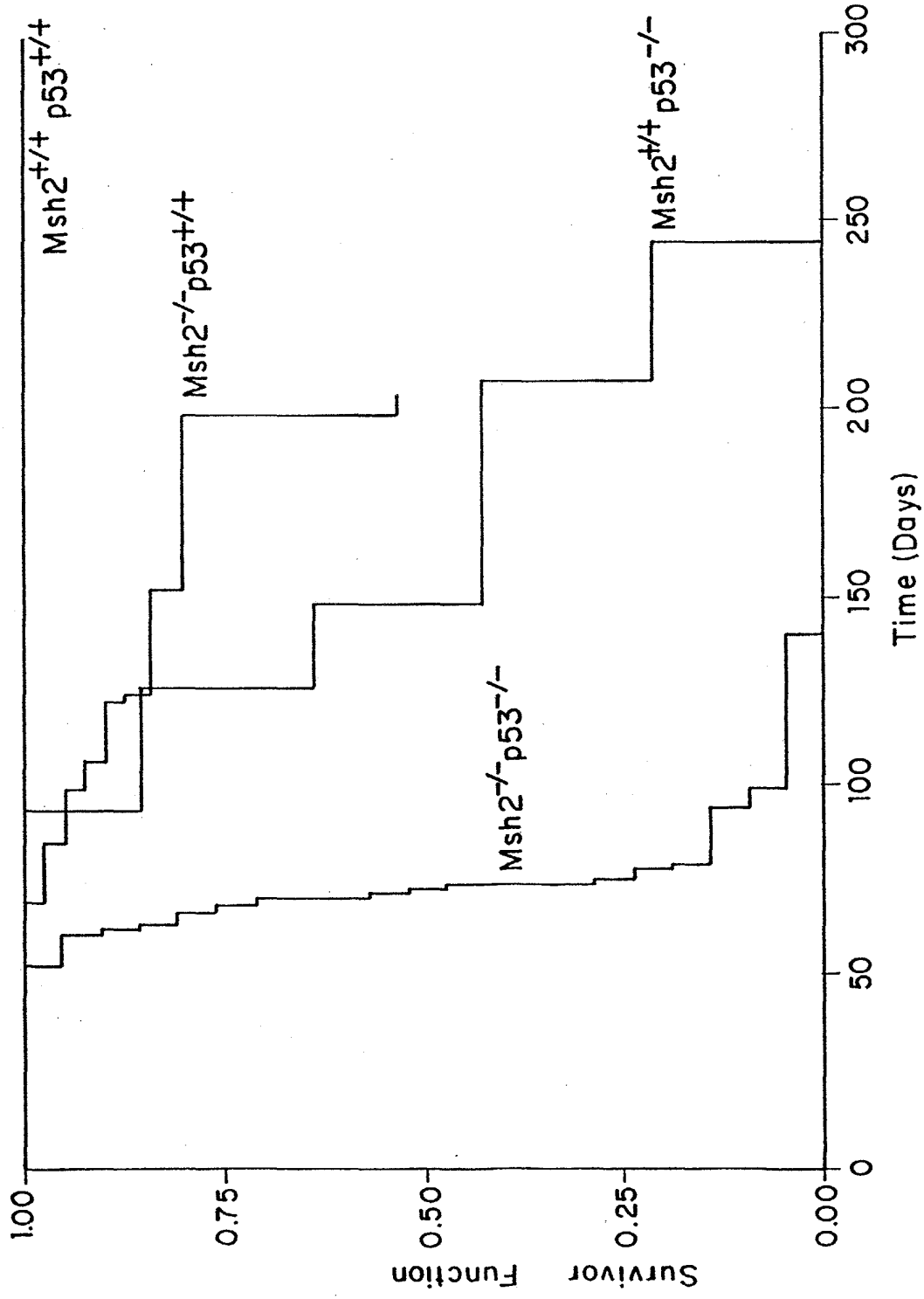

Msh2+/+ p53+/+
Msh2-/-p53+/+
Msh2+/+ p53-/-
Msh2-/-p53-/-
Survivor Function
1.00
0.75
0.50
0.25
0.00
0
50
100
150
200
250
300
Time (Days)

FIG. 11

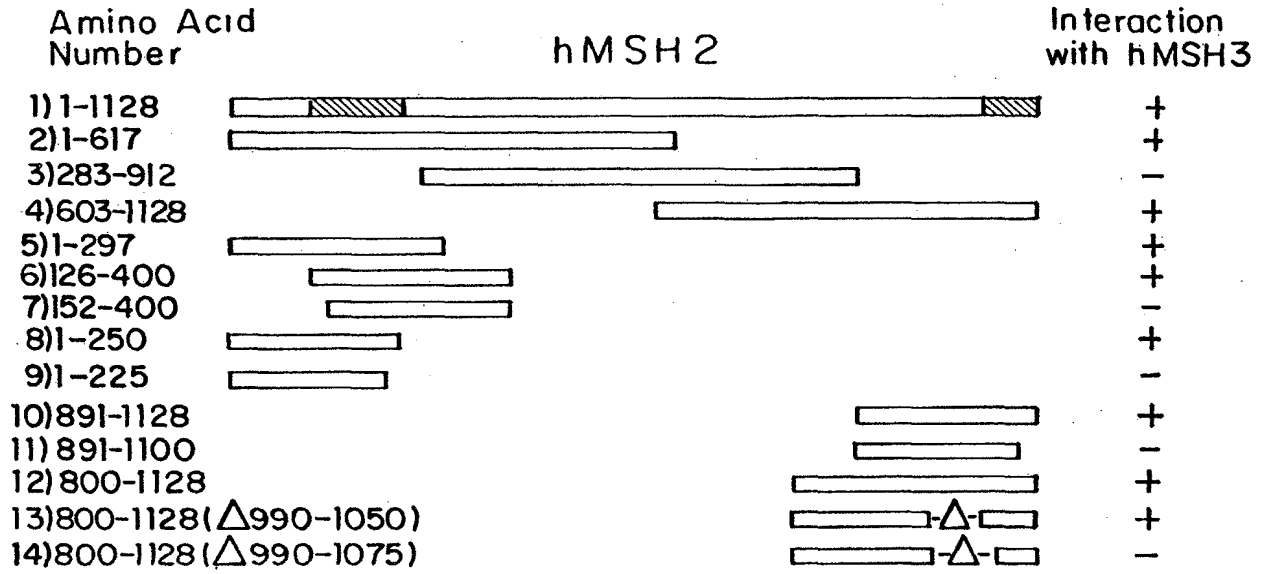


FIG. 12

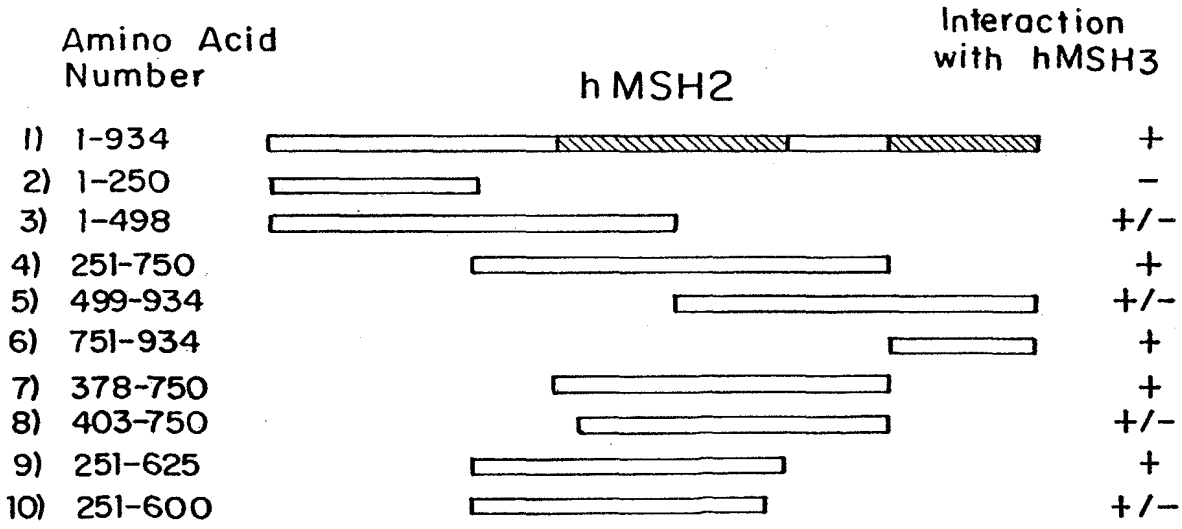


FIG. 13

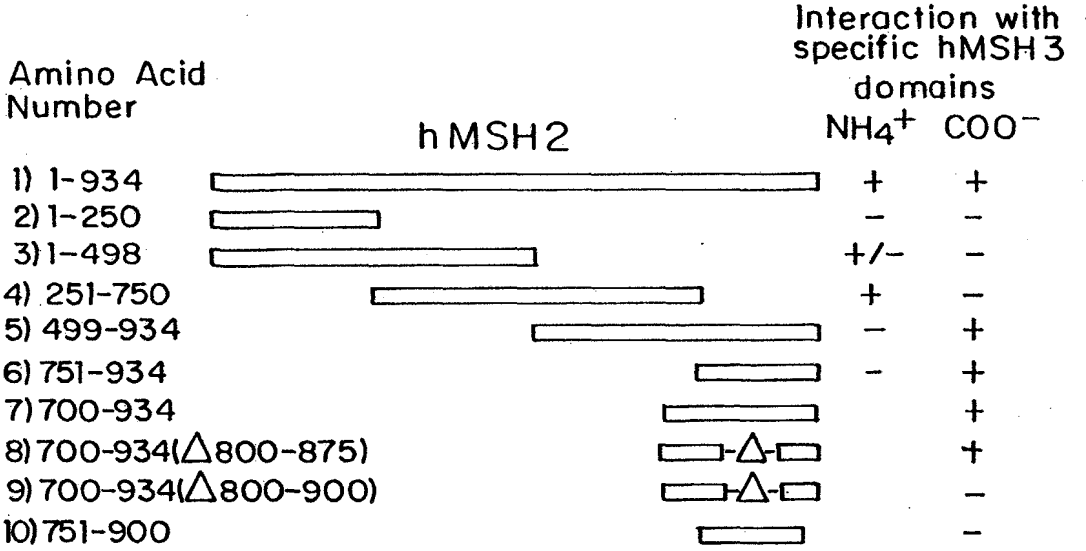

Amino Acid Number
hMSH2
Interaction with specific hMSH3 domains
NH4+ COO−
1) 1-934 + +
2) 1-250 − −
3) 1-498 +/− −
4) 251-750 + −
5) 499-934 − +
6) 751-934 − +
7) 700-934 +
8) 700-934(Δ800-875) +
9) 700-934(Δ800-900) −
10) 751-900 −

FIG. 14

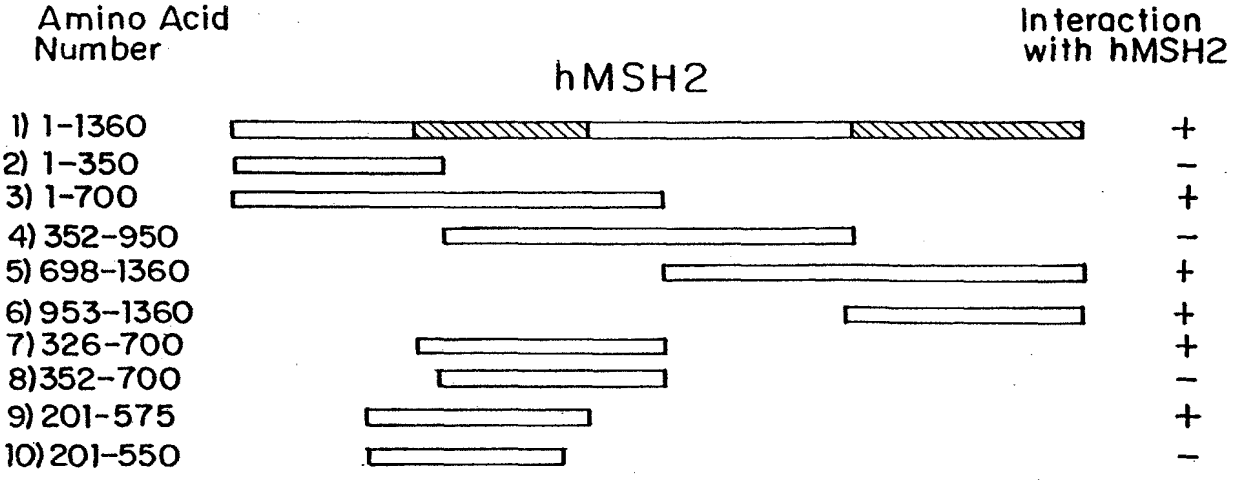

Amino Acid Number
hMSH2
Interaction with hMSH2
1) 1-1360 +
2) 1-350 −
3) 1-700 +
4) 352-950 −
5) 698-1360 +
6) 953-1360 +
7) 326-700 +
8) 352-700 −
9) 201-575 +
10) 201-550 −

FIG. 15

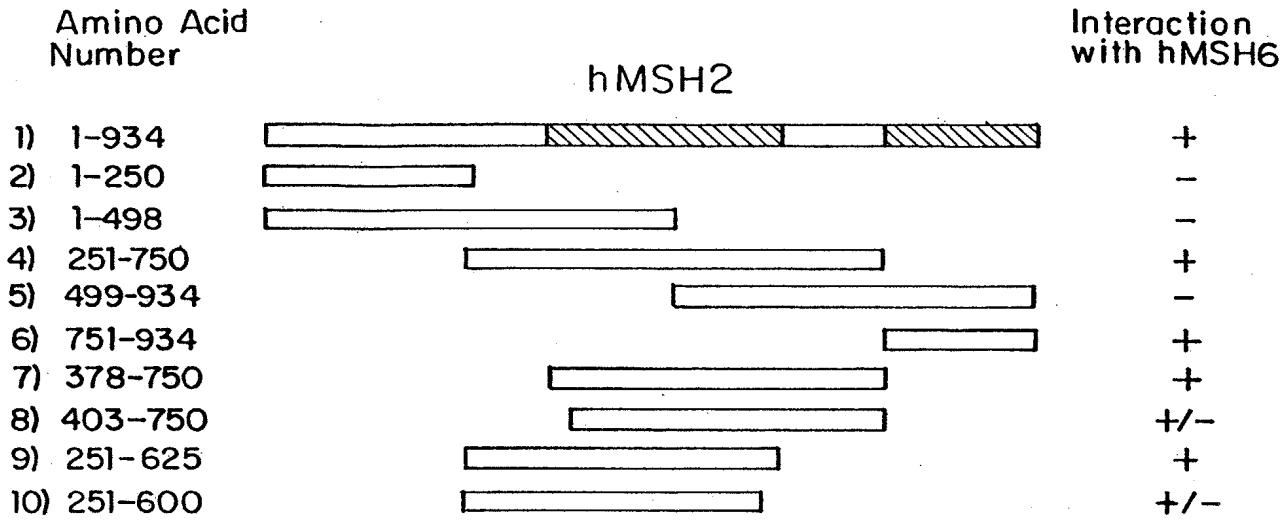

Amino Acid Number
hMSH2
Interaction with hMSH6
1) 1-934 +
2) 1-250 –
3) 1-498 –
4) 251-750 +
5) 499-934 –
6) 751-934 +
7) 378-750 +
8) 403-750 +/–
9) 251-625 +
10) 251-600 +/–

FIG. 16

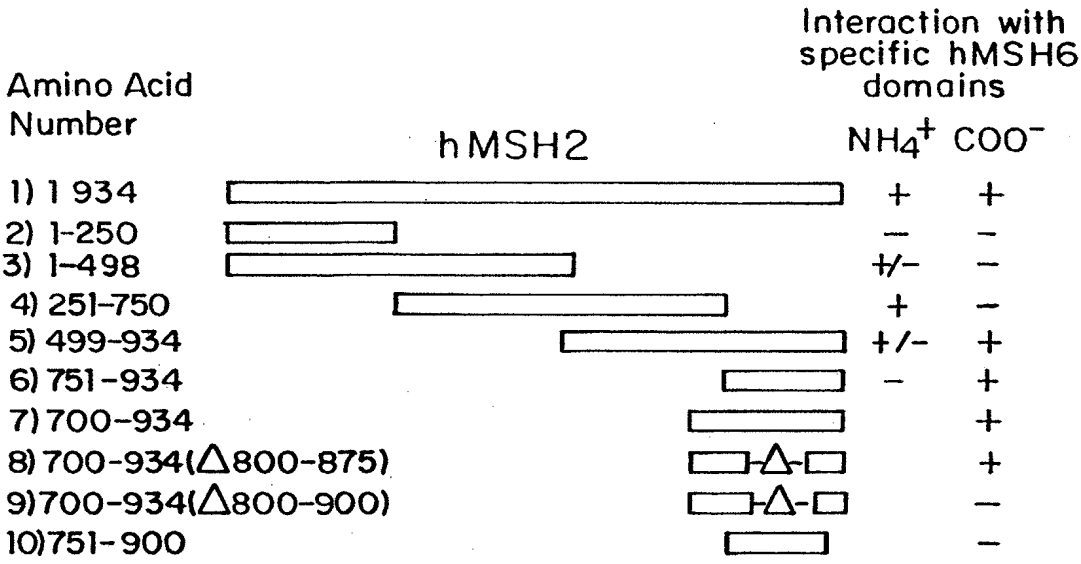

Interaction with specific hMSH6 domains
Amino Acid Number
hMSH2
NH4+ COO-
1) 1 934 + +
2) 1-250 – –
3) 1-498 +/– –
4) 251-750 + –
5) 499-934 +/– +
6) 751-934 – +
7) 700-934 +
8) 700-934(Δ800-875) +
9) 700-934(Δ800-900) –
10) 751-900 –

FIG. 17

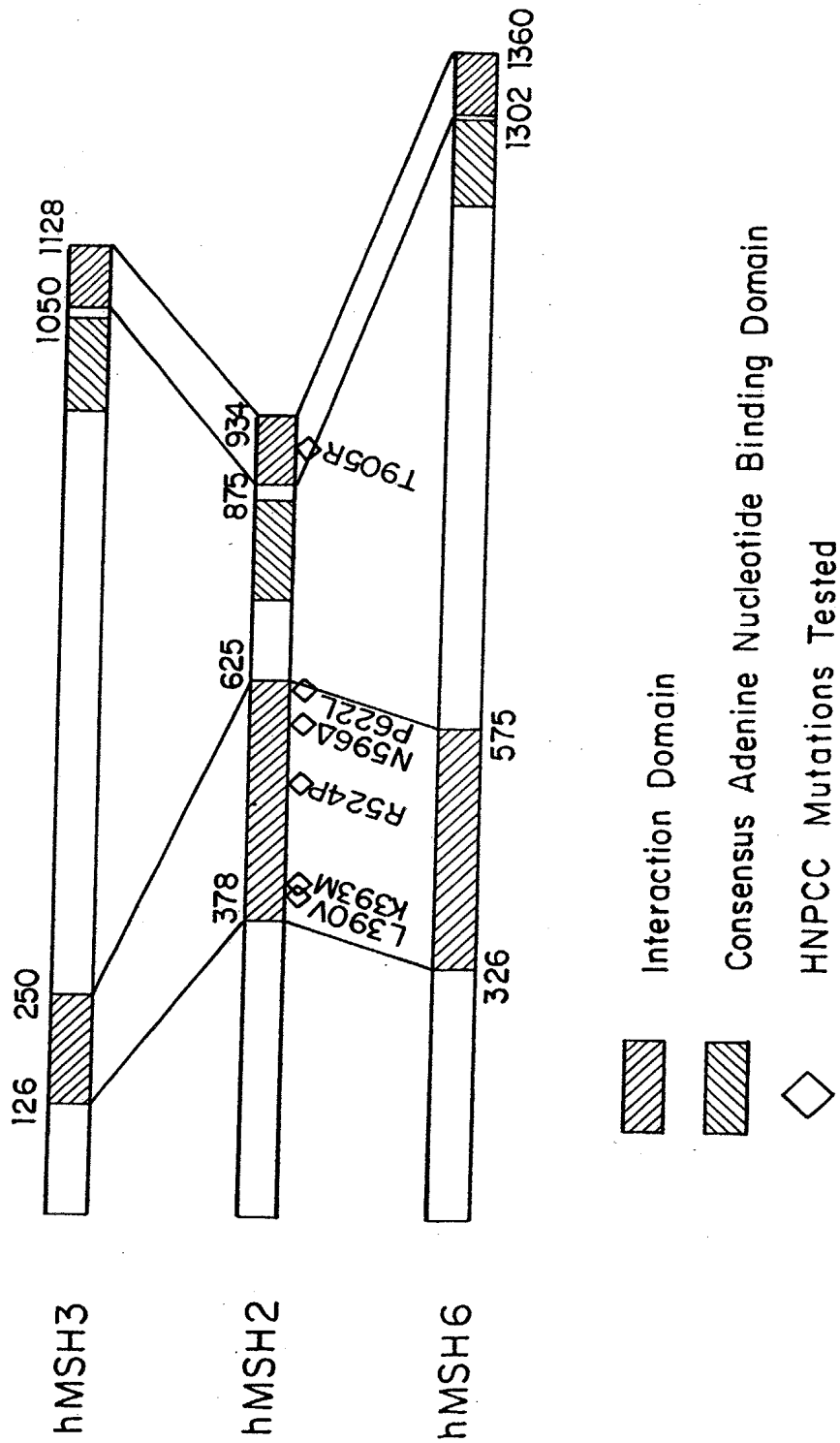

hMSH3
hMSH2
hMSH6
126
250
1050
1128
378
625
875
934
1302
1360
326
575
T905R
P622L
N596A
R524P
K393M
L390V
Interaction Domain
Consensus Adenine Nucleotide Binding Domain
HNPCC Mutations Tested

FIG. 18

```
  1                  CAGAAACCTCATACTTCTCGGGTCAGGGAAGGTTTGGGAGGGC
 44 GTGGCGGTCGGTCAGCGGGGCGTTCTCCCACCTGTAGCGACTCAGAGCCTCCAAGCTC

  1 Met Ala Ser Leu Gly Ala Asn Pro Arg Arg Thr Pro Gln Gly Pro
102 ATG GCC TCC TTA GGA GCG AAC CCA AGG AGG ACA CCG CAG GGA CCG

 16 Arg Pro Gly Ala Ala Ser Ser Gly Phe Pro Ser Pro Ala Pro Val
147 AGA CCT GGG GCG GCC TCC TCC GGC TTC CCC AGC CCG GCC CCA GTG

 31 Pro Gly Pro Arg Glu Ala Glu Glu Glu Glu Val Glu Glu Glu Glu
192 CCG GGC CCC AGG GAG GCC GAG GAG GAG GAA GTC GAG GAG GAG GAG

 46 Glu Leu Ala Glu Ile His Leu Cys Val Leu Trp Asn Ser Gly Tyr
237 GAG CTG GCC GAG ATC CAT CTG TGT GTG CTG TGG AAT TCA GGA TAC

 61 Leu Gly Ile Ala Tyr Tyr Asp Thr Ser Asp Ser Thr Ile His Phe
282 TTG GGC ATT GCC TAC TAT GAT ACT AGT GAC TCC ACT ATC CAC TTC

 76 Met Pro Asp Ala Pro Asp His Glu Ser Leu Lys Leu Leu Gln Arg
327 ATG CCA GAT GCC CCA GAC CAC GAG AGC CTC AAG CTT CTC CAG AGA

 91 Val Leu Asp Glu Ile Asn Pro Gln Ser Val Val Thr Ser Ala Lys
372 GTT CTG GAT GAG ATC AAT CCC CAG TCT GTT GTT ACG AGT GCC AAA

106 Gln Asp Glu Asn Met Thr Arg Phe Leu Gly Lys Leu Ala Ser Gln
417 CAG GAT GAG AAT ATG ACT CGA TTT CTG GGA AAG CTT GCC TCC CAG
```

Fig. 19A

```
121 Glu His Arg Glu Pro Lys Arg Pro Glu Ile Ile Phe Leu Pro Ser
462 GAG CAC AGA GAG CCT AAA AGA CCT GAA ATC ATA TTT TTG CCA AGT

136 Val Asp Phe Gly Leu Glu Ile Ser Lys Gln Arg Leu Leu Ser Gly
507 GTG GAT TTT GGT CTG GAG ATA AGC AAA CAA CGC CTC CTT TCT GGA

151 Asn Tyr Ser Phe Ile Pro Asp Ala Met Thr Ala Thr Glu Lys Ile
552 AAC TAC TCC TTC ATC CCA GAC GCC ATG ACT GCC ACT GAG AAA ATC

166 Leu Phe Leu Ser Ser Ile Ile Pro Phe Asp Cys Leu Leu Thr Val
597 CTC TTC CTC TCT TCC ATT ATT CCC TTT GAC TGC CTC CTC ACA GTT

181 Arg Ala Leu Gly Gly Leu Leu Lys Phe Leu Gly Arg Arg Arg Ile
642 CGA GCA CTT GGA GGG CTG CTG AAG TTC CTG GGT CGA AGA AGA ATC

196 Gly Val Glu Leu Glu Asp Tyr Asn Val Ser Val Pro Ile Leu Gly
687 GGG GTT GAA CTG GAA GAC TAT AAT GTC AGC GTC CCC ATC CTG GGC

211 Phe Lys Lys Phe Met Leu Thr His Leu Val Asn Ile Asp Gln Asp
732 TTT AAG AAA TTT ATG TTG ACT CAT CTG GTG AAC ATA GAT CAA GAC

226 Thr Tyr Ser Val Leu Gln Ile Phe Lys Ser Glu Ser His Pro Ser
777 ACT TAC AGT GTT CTA CAG ATT TTT AAG AGT GAG TCT CAC CCC TCA

241 Val Tyr Lys Val Ala Ser Gly Leu Lys Glu Gly Leu Ser Leu Phe
822 GTG TAC AAA GTG GCC AGT GGA CTG AAG GAG GGG CTC AGC CTC TTT
```

Fig. 19B

```
256 Gly Ile Leu Asn Arg Cys His Cys Lys Trp Gly Glu Lys Leu Leu
867 GGA ATC CTC AAC AGA TGC CAC TGT AAG TGG GGA GAG AAG CTG CTC

271 Arg Leu Trp Phe Thr Arg Pro Thr His Asp Leu Gly Glu Leu Ser
912 AGG CTA TGG TTC ACA CGT CCG ACT CAT GAC CTG GGG GAG CTC AGT

286 Ser Arg Leu Asp Val Ile Gln Phe Phe Leu Leu Pro Gln Asn Leu
957 TCT CGT CTG GAC GTC ATT CAG TTT TTT CTG CTG CCC CAG AAT CTG

301 Asp Met Ala Gln Met Leu His Arg Leu Leu Gly His Ile Lys Asn
1002 GAC ATG GCT CAG ATG CTG CAT CGG CTC CTG GGT CAC ATC AAG AAC

316 Val Pro Leu Ile Leu Lys Arg Met Lys Leu Ser His Thr Lys Val
1047 GTG CCT CTG ATT CTG AAA CGC ATG AAG TTG TCC CAC ACC AAG GTC

331 Ser Asp Trp Gln Val Leu Tyr Lys Thr Val Tyr Ser Ala Leu Gly
1092 AGC GAC TGG CAG GTT CTC TAC AAG ACT GTG TAC AGT GCC CTG GGC

346 Leu Arg Asp Ala Cys Arg Ser Leu Pro Gln Ser Ile Gln Leu Phe
1137 CTG AGG GAT GCC TGC CGC TCC CTG CCG CAG TCC ATC CAG CTC TTT

361 Arg Asp Ile Ala Gln Glu Phe Ser Asp Asp Leu His His Ile Ala
1182 CGG GAC ATT GCC CAA GAG TTC TCT GAT GAC CTG CAC CAT ATC GCC

376 Ser Leu Ile Gly Lys Val Val Asp Phe Glu Gly Ser Leu Ala Glu
1227 AGC CTC ATT GGG AAA GTA GTG GAC TTT GAG GGC AGC CTT GCT GAA
```

Fig. 19C

```
 391 Asn Arg Phe Thr Val Leu Pro Asn Ile Asp Pro Glu Ile Asp Glu
1272 AAT CGC TTC ACA GTC CTC CCC AAC ATA GAT CCT GAA ATT GAT GAG

 406 Lys Lys Arg Arg Leu Met Gly Leu Pro Ser Phe Leu Thr Glu Val
1317 AAA AAG CGA AGA CTG ATG GGA CTT CCC AGT TTC CTT ACT GAG GTT

 421 Ala Arg Lys Glu Leu Glu Asn Leu Asp Ser Arg Ile Pro Ser Cys
1362 GCC CGC AAG GAG CTG GAG AAT CTG GAC TCC CGT ATT CCT TCA TGC

 436 Ser Val Ile Tyr Ile Pro Leu Ile Gly Phe Leu Leu Ser Ile Pro
1407 AGT GTC ATC TAC ATC CCT CTG ATT GGC TTC CTT CTT TCT ATT CCC

 451 Arg Leu Pro Ser Met Val Glu Ala Ser Asp Phe Glu Ile Asn Gly
1452 CGC CTG CCT TCC ATG GTA GAG GCC AGT GAC TTT GAG ATT AAT GGA

 466 Leu Asp Phe Met Phe Leu Ser Glu Glu Lys Leu His Tyr Arg Ser
1497 CTG GAC TTC ATG TTT CTC TCA GAG GAG AAG CTG CAC TAT CGT AGT

 481 Ala Arg Thr Lys Glu Leu Asp Ala Leu Leu Gly Asp Leu His Cys
1542 GCC CGA ACC AAG GAG CTG GAT GCA TTG CTG GGG GAC CTG CAC TGC

 496 Glu Ile Arg Asp Gln Glu Thr Leu Leu Met Tyr Gln Leu Gln Cys
1587 GAG ATC CGG GAC CAG GAG ACG CTG CTG ATG TAC CAG CTA CAG TGC

 511 Gln Val Leu Ala Arg Ala Ala Val Leu Thr Arg Val Leu Asp Leu
1632 CAG GTG CTG GCA CGA GCA GCT GTC TTA ACC CGA GTA TTG GAC CTT
```

Fig. 19D

```
 526 Ala Ser Arg Leu Asp Val Leu Leu Ala Leu Ala Ser Ala Ala Arg
1677 GCC TCC CGC CTG GAC GTC CTG CTG GCT CTT GCC AGT GCT GCC CGG

 541 Asp Tyr Gly Tyr Ser Arg Pro Arg Tyr Ser Pro Gln Val Leu Gly
1722 GAC TAT GGC TAC TCA AGG CCG CGT TAC TCC CCA CAA GTC CTT GGG

 556 Val Arg Ile Gln Asn Gly Arg His Pro Leu Met Glu Leu Cys Ala
1767 GTA CGA ATC CAG AAT GGC AGA CAT CCT CTG ATG GAA CTC TGT GCC

 571 Arg Thr Phe Val Pro Asn Ser Thr Glu Cys Gly Gly Asp Lys Gly
1812 CGA ACC TTT GTG CCC AAC TCC ACA GAA TGT GGT GGG GAC AAA GGG

 586 Arg Val Lys Val Ile Thr Gly Pro Asn Ser Ser Gly Lys Ser Ile
1857 AGG GTC AAA GTC ATC ACT GGA CCC AAC TCA TCA GGG AAG AGC ATA

 601 Tyr Leu Lys Gln Val Gly Leu Ile Thr Phe Met Ala Leu Val Gly
1902 TAC CTC AAA CAG GTA GGC TTG ATC ACA TTC ATG GCC CTG GTA GGC

 616 Ser Phe Val Pro Ala Glu Glu Ala Glu Ile Gly Ala Val Asp Ala
1947 AGC TTT GTG CCA GCA GAG GAG GCC GAA ATT GGG GCA GTA GAC GCC

 631 Ile Phe Thr Arg Ile His Ser Cys Glu Ser Ile Ser Leu Gly Leu
1992 ATC TTC ACA CGA ATT CAT AGC TGC GAA TCC ATC TCC CTT GGC CTC

 646 Ser Thr Phe Met Ile Asp Leu Asn Gln Val Ala Lys Ala Val Asn
2037 TCC ACC TTC ATG ATC GAC CTC AAC CAG GTG GCG AAA GCA GTG AAC
```

Fig. 19E

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 661 Asn Ala Thr Ala Gln Ser Leu Val Leu Ile Asp Glu Phe Gly Lys
2082 AAT GCC ACT GCA CAG TCG CTG GTC CTT ATT GAT GAA TTT GGA AAG

 676 Gly Thr Asn Thr Val Asp Gly Leu Ala Leu Leu Ala Ala Val Leu
2127 GGA ACC AAC ACG GTG GAT GGG CTC GCG CTT CTG GCC GCT GTG CTC

 691 Arg His Trp Leu Ala Arg Gly Pro Thr Cys Pro His Ile Phe Val
2172 CGA CAC TGG CTG GCA CGT GGA CCC ACA TGC CCC CAC ATC TTT GTG

706 Ala Thr Asn Phe Leu Ser Leu Val Gln Leu Gln Leu Leu Pro Gln
2217 GCC ACC AAC TTT CTG AGC CTT GTT CAG CTA CAA CTG CTG CCA CAA

 721 Gly Pro Leu Val Gln Tyr Leu Thr Met Glu Thr Cys Glu Asp Gly
2262 GGG CCC CTG GTG CAG TAT TTG ACC ATG GAG ACC TGT GAG GAT GGC

 736 Asn Asp Leu Val Phe Phe Tyr Gln Val Cys Glu Gly Val Ala Lys
2307 AAC GAT CTT GTC TTC TTC TAT CAG GTT TGC GAA GGT GTT GCG AAG

 751 Ala Ser His Ala Ser His Thr Ala Ala Gln Ala Gly Leu Pro Asp
2352 GCC AGC CAT GCC TCC CAC ACA GCT GCC CAG GCT GGG CTT CCT GAC

 766 Lys Leu Val Ala Arg Gly Lys Glu Val Ser Asp Leu Ile Arg Ser
2397 AAG CTT GTG GCT CGT GGC AAG GAG GTC TCA GAC TTG ATC CGC AGT

 781 Gly Lys Pro Ile Lys Pro Val Lys Asp Leu Leu Lys Lys Asn Gln
2442 GGA AAA CCC ATC AAG CCT GTC AAG GAT TTG CTA AAG AAG AAC CAA
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Fig. 19F

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 796 Met Glu Asn Cys Gln Thr Leu Val Asp Lys Phe Met Lys Leu Asp
2487 ATG GAA AAT TGC CAG ACA TTA GTG GAT AAG TTT ATG AAA CTG GAT

 811 Leu Glu Asp Pro Asn Leu Asp Leu Asn Val Phe Met Ser Gln Glu
2532 TTG GAA GAT CCT AAC CTG GAC TTG AAC GTT TTC ATG AGC CAG GAA

 826 Val Leu Pro Ala Ala Thr Ser Ile Leu Stop
2577 GTG CTG CCT GCT GCC ACC AGC ATC CTC TGA GAGTCCTTCCAGTGTCCTC

2626 CCCAGCCTCCTGAGACTCCGGTGGGCTGCCATGCCCTCTTTGTTTCCTTATCTCCCTCA
2686 GACGCAGAGTTTTTAGTTTCTCACAATTCTAATGTAATAATATATCTTAA
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Fig. 19G